

A DEMONSTRATION OF A DEPRESSOR SUBSTANCE IN THE SERUM OF THE BLOOD OF PATIENTS AFFECTED WITH EXOPHTHALMIC GOITER.¹

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DURING the past year we have conducted a series of experiments with a view to throwing further light on the relation of the secretion of the thyroid to exophthalmic goiter. We have studied chiefly the cardiovascular effects on the dog of intravenous injections of sterile non-hemolytic blood-serum from nervous individuals and from patients affected with exophthalmic goiter. Also, numerous saline extracts of goiter have been injected intravenously into dogs and the effects on the blood pressure studied.

Gley², in 1911, announced that the serum of certain cases of exophthalmic goiter produces marked cardiac depressor action. He showed, too, that a first injection of potent exophthalmic serum conferred a tolerance of such a nature that subsequent injections of the same serum during the same experiment produced little or no effect.

We have attempted to follow out Gley's researches, injecting intravenously into dogs the serum procured from patients affected with exophthalmic goiter. The effect on blood-pressure was recorded graphically on a long paper kymograph in the usual manner, using the left carotid artery for the arterial cannula. All injections were made into the right femoral vein. The right vagus was exposed and stimulated by induction shock in certain experiments. Blood was obtained by sterile technic from the median basilic veins of the patients, collected in sterile flasks and the serum allowed to separate in the cold. The manifest difficulty that must always be encountered in such work, *i. e.*, the impracticability of obtaining a large supply of blood from each case, has somewhat hindered certain experiments, but we believe that our results are sufficiently interesting to justify reporting.

Gley states that 5 c.c. of serum per kilo dog weight must be used to obtain the best results. We did not have sufficient serum for such large dosage, but obtained excellent results with smaller doses. We have injected $2\frac{1}{2}$ to 4 c.c. serum per kilo dog weight as an average dose, and except when stated to the contrary, this has been the amount of serum.

¹ Read before the Association of American Physicians, Washington, D. C., May, 1913.

² Jour. de Phys. et de Path. Gén., 1911, xiii, 928 to 941; Cleret, *ibid.*, pp. 955 to 970.

We have used for these experiments the sera from twenty-eight patients having exophthalmic goiter. Other sera examined have included those from normal individuals, from patients having goiters without apparent intoxication, and from patients presenting the picture of a long-standing intoxication, presumably due to adenomas of the thyroid. Only the sera from patients with active symptoms of exophthalmic goiter and with markedly hyperplastic glands, as shown by microscopic examination have produced in the dogs injected any definite symptoms of cardiovascular depression.

The curves produced by the sera from patients affected with exophthalmic goiter have naturally fallen into three groups:

Group I. Those sera causing more than 30 mm. of Hg. drop in blood-pressure.

Group II. Those sera causing a drop in blood-pressure, but less than 30 mm. of Hg.

Group III. Those sera causing no appreciable drop in blood-pressure.

The significance of this classification was observed only after an analysis of the individual cases.

Group I. *Six Sera Causing Drops in Blood Pressure of More than 30 mm. of Hg.* The four curves in Chart 1, all of which produced drops in blood-pressure of more than 30 mm. of Hg. when injected in doses of 2.5 c.c. per kilo dog weight, were obtained by injecting sera from patients who were at or near the height of an early and severe intoxication, as shown by the following summaries of the case histories:

CASE 69,123.—Female, aged twenty years. Three months before (March, 1912) noticed suddenly all the typical cardiac, nervous, and muscular symptoms of Graves' disease. Rapid progress during one month to acute vomiting, with great loss of strength. During the third month vomiting ceased, but all other symptoms were marked. (Experiment conducted on dog 253.)

CASE 69,198.—Female, aged fifty years. Slight goiter noted one year before (May, 1911). Definite typical symptoms of exophthalmic goiter began six months before with loss of weight, weakness, and nervousness. Two months before violent crisis, with vomiting, the patient remaining in an acute condition for one week, since then vomiting in spells. In bed most of the time. Loss of thirty pounds in weight in two months. Patient had not noted exophthalmos, which was moderately evident. (Experiment conducted on dog 259.)

CASE 67,993.—Male, aged seventeen years. Three months before (February, 1912) began to lose weight, and all the usual symptoms became evident and rapidly progressed. A month later goiter was noted and the patient forced to bed by weakness. In bed one month, then slight improvement, and has been able to be out of

bed the past month, though a marked intoxication is still present. (Experiment conducted on dog 249.)

CASE 68,628.—Female, aged twenty-three years. Six months before (January, 1912) developed nervous and cardiac symptoms and exophthalmos. She rapidly became worse, and at present shows marked intoxication. Diarrhea for one month. Marked loss of strength and fifteen pounds loss of weight. This patient died in an exacerbation following a single ligation. Unfortunately autopsy on this patient was refused. (Experiment conducted on dog 192.)

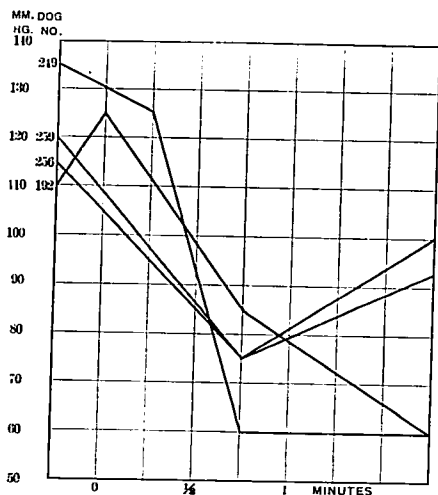


CHART 1.—Drops in blood-pressure of more than 30 mm. after injection of sera from patients in the stage of acute intoxication from exophthalmic goiter.

We believe these histories show conclusively that the four cases were all acute and severe intoxications. Clinical diagnoses in these as well as the following cases have been confirmed by pathological examination of the goiters except the one which terminated fatally.

The two cases shown in Chart 2 are interesting exceptions. One was a fairly acute intoxication of only moderate severity; the other was a chronic intoxication of marked severity. The case histories are as follows:

CASE 75,496. Male, mulatto, aged thirty years. Past history, gonorrhea, syphilis (positive Wassermann), and some alcoholic excess. Two years before (November, 1910) began to lose weight

and strength, and noticed nervous, cardiac, and eye symptoms. Rapid progress to an extreme crisis, with prostration, vomiting, and diarrhea. Then recovery during six months; able to do some work, but still had marked intoxication with a chronic diarrhea.

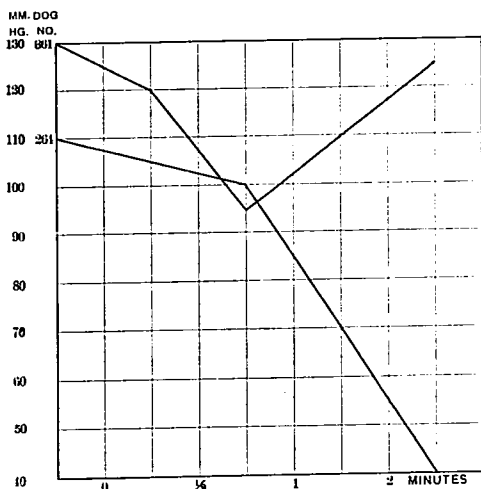


CHART 2.—Drops in blood-pressure of more than 30 mm. after injection of large doses of sera from patients with moderate intoxication from exophthalmic goiter.

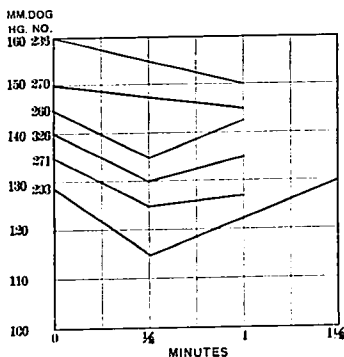


CHART 3.—Drops in blood-pressure of less than 30 mm. after injection of sera from patients not at the height of intoxication from exophthalmic goiter.

Weight forty pounds below normal. (Experiment conducted on dog 361.)

CASE 69,619.—Female, aged nineteen years. Nine months before (October, 1911) had to stop school on account of weakness, dyspnea and nervousness. Symptoms progressively worse until forced to bed six months before. After a rest she improved steadily, and presents a clean-cut but not marked picture of exophthalmic goiter. (Experiment conducted on dog 264.)

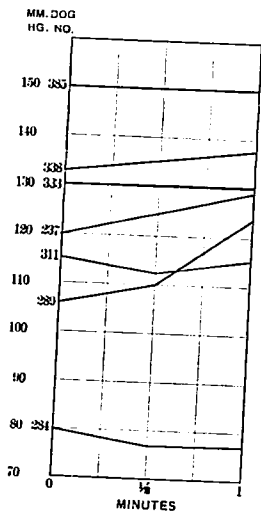


CHART 4.—No effect on blood-pressure following injection of sera from patients with symptoms of intoxication from exophthalmic goiter, but not at or near crisis.

From the two preceding histories we may judge that neither case was extreme. On examining our records we find that the doses of serum given each dog were about three times that used to secure the marked effects shown in Chart 1. Again, we may note that the first case (75,496) was a chronic and severe one, but gave only a 35 mm. drop in blood-pressure, thus almost admitting it into the next group. The second case (69,619) gave a marked fall in blood-pressure, and though not very severe, was not far past a crisis when the blood was taken.

Group II. *Ten Sera Causing Drops in Blood Pressure of Less than 30 mm. of Hg.* Chart 3 shows the curves resulting from injections of six of these sera which caused a fall in blood-pressure of less than 30 mm. of Hg., but which apparently contained a slight amount of the depressor agent. Eight of these ten patients had

been afflicted with the disease for more than a year and none of them seemed near any marked exacerbation. In general it may be stated that these cases were of longer standing and with more pronounced intoxication than those in the following group. Two typical histories from this group are as follows:

CASE 68,883.—Male, aged thirty years. Appendectomy had been done eighteen months before (January, 1910), following which symptoms of exophthalmic goiter promptly appeared and progressed during six months to an extreme intoxication with vomiting, diarrhea, and prostration. Loss of forty pounds in six months. For the past six months steady improvement, and now is nearly normal in weight, though still affected with definite Graves' disease. (Experiment conducted on dog 253.)

CASE 67,283.—Female, aged thirty-six years. Tremor noted for several years. Always more or less nervous. Increased irritability and gradual loss of strength was noted six months before (November, 1911). No dyspnea. Slight diarrhea during the past month. Working steadily to date. (Experiment conducted on dog 236.)

Thirteen Sera Causing no Appreciable Drop in Blood-pressure. Chart 4 shows six curves as typical of the thirteen inert sera which fall into this group. None of the patients seemed to be near a crisis, and eight of them had been sick less than nine months.

These experiments seem to indicate that patients affected with exophthalmic goiter who are suffering from a marked degree of intoxication at or near the height of the clinical curve of the disease (Plummer) possess serum which has a powerful depressor action. The authors have failed to demonstrate this depressor action by similar means in normal sera, or in sera from patients not having markedly hyperplastic thyroids. Also sera from patients with exophthalmic goiter not at or near the crest of the wave of intoxication are less potent or may be entirely inactive.

Since it was not always thought best to bleed very sick patients, only a small number of experiments have been made with sera from patients with severe intoxications. Yet it may be of interest to know that most of the patients that were bled experienced considerable relief from their subjective symptoms after the bleeding.

The results of intravenous injections into dogs of saline extract of ninety goiters of various kinds from human patients have also been made. These experiments may have some bearing on the action of the depressor sera and a brief report of the results is herewith appended.

Intravenous Injections of Saline Extracts. Experiments with extracts of forty-eight exophthalmic thyroids have shown that the markedly hyperplastic goiters considered typical of Graves' disease have a more powerful depressor action than that of the extract of any normal organ examined, including muscle, liver, spleen, pancreas, breast, testicle, thyroid, etc. The fall in blood-pressure

averages 60 mm. of Hg., and is often considerably more, whereas that from other tissues in any comparable dosage is usually less than 25 mm.

Extracts of adenomas of the thyroid, of simple colloid goiters, and of normal thyroids likewise have a depressor action, which, however, has not been found so marked as that produced by extracts of exophthalmic thyroids. Injections equivalent to as much as 5 gm. per kilo dog weight do not cause a fall as great as that of the extracts of exophthalmic goiters in doses of 0.5 gm. per kilo dog weight.

The first injection of any extract of fresh goiter, as of most extracts of tissue, confers a marked degree of tolerance to subsequent injections of the same material during the same experiment.

As is well known, peptone solutions cause a marked fall in blood-pressure on intravenous injection, and subsequent injections show that a tolerance has been established similar to that produced by extracts from goiters. The depressor action of peptone solution is not, however, affected by a previous dose of the extract of exophthalmic goiter, nor is the action of the extract of exophthalmic goiter affected by a previous dose of peptone solution. On the other hand, it is interesting to note that the depressor action of the extract of an exophthalmic goiter is much diminished by a previous dose of potent serum from a case of toxic exophthalmic goiter, and the reverse, judging from a limited number of experiments, is equally true. In other words, a crossed tolerance seems to exist between the depressor action of extract of exophthalmic goiter and of exophthalmic serum. It seems probable, therefore, that the depressor agent in the extract of exophthalmic thyroid and that in the serum from a case of exophthalmic goiter are of the same nature.

No attempt has yet been made to identify the chemical nature of the depressor substances in these extracts of thyroids or of those in sera of patients affected with exophthalmic goiter. From certain experimental evidence it seems that the substance is neither cholin nor ordinary peptone.

CONCLUSIONS. We believe that the work submitted justifies the following conclusions:

Fresh extracts made from exophthalmic thyroids contain a powerful depressor substance.

A powerful depressor substance likewise exists in the sera obtained from certain cases of exophthalmic goiter.

The latter substance is present in direct proportion to the clinical acuteness and severity of the disease.

The sera from patients with non-hyperplastic thyroids do not have a depressor action.

After an active depressor dose of the serum from a case of exophthalmic goiter the depressor action of the extract of an exophthalmic goiter is weakened or abolished. The converse is also true.